Biol Blood Marrow Transplant 21 (2015) 275–280

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

Oral Manifestations Compatible with Chronic Graft-versus-Host Disease in Patients with Fanconi Anemia

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Article history:
Received 30 July 2014
Accepted 7 October 2014

Key Words:
Fanconi anemia
Bone marrow transplantation
Graft-versus-host disease
Mouth
Mucosa
Consensus Development Conference
National Institutes of Health

A B S T R A C T

Fanconi anemia (FA) is a genetic disease that is characterized by several congenital abnormalities and progressive bone marrow failure and is associated with an increased susceptibility to malignant disorders. Currently, the only potential cure for hematological disorders is hematopoietic stem cell transplantation (HSCT). However, 1 of the most common complications after HSCT is the development of oral chronic graft-versus-host disease (cGVHD), which is also a risk factor for the development of cancer, particularly oral squamous cell carcinoma. Therefore, the purpose of this study was to describe the prevalence and characteristics of oral manifestations compatible with cGVHD in patients diagnosed with FA according to the National Institutes of Health (NIH) consensus criteria. A total of 96 patients (51 females, 45 males; median age, 16 years) with FA, who were in medical follow-up after HSCT at the outpatient clinic of the bone marrow transplantation unit (Hospital de Clínicas from the Universidade Federal do Paraná) underwent an oral evaluation between January 2013 and December 2013. Post-HSCT periods varied from 1 to 261 months and were divided into 3 periods: immediate post-HSCT period; intermediate post-HSC period, and late post-HSCT period. Among the evaluated patients, 40 of 96 (42%) presented with oral manifestations of cGVHD, with 29 of 40 (73%) of these patients in the late post-HSCT period. NIH scale scores varied from 0 to 10, and lichenoid and hyperkeratotic lesions were the abnormalities most frequently observed (100%). Overall, a high prevalence of oral manifestations was observed for cGVHD patients with FA. These data highlight the importance of monitoring oral manifestations compatible with cGVHD to identify and treat individuals with a higher risk of developing oral cancer.

INTRODUCTION

Fanconi anemia (FA) is a rare genetic disease that is related to chromosomal instability and the defective repair of DNA damage [1,2]. FA is also characterized by congenital malformations, progressive bone marrow failure, and a 700-fold increase in the risk for head and neck squamous cell carcinoma (SCC) [1-3].

Currently, hematopoietic stem cell transplantation (HSCT) is the only potential cure for hematologic disorders related to FA [3,4]. However, after this procedure, patients have an additional 4-fold higher risk for head and neck SCC [5]. Moreover, patients subjected to HSCT are susceptible to chronic graft-versus-host disease (cGVHD), which is a common alloimmune and autoimmune complication [6]. Individuals with cGVHD can present with hyperkeratotic and lichenoid lesions in the mouth, erythema, ulcers, atrophy, and pain [7]. Patients with cGVHD also have an increased risk of developing malignancies [8-10].

Therefore, the purpose of this study was to evaluate the prevalence of oral manifestations of cGVHD in FA patients who underwent allogeneic HSCT, according to the National Institutes of Health (NIH) consensus criteria [7], and to describe the characteristics and distribution of these manifestations in the mouth.

MATERIALS AND METHODS

This cross-sectional study was performed between January 2013 and December 2013. Patients, regardless of age, with a confirmed FA diagnosis (positive diepoxy-butane test), who were subjected to allogeneic HSCT and underwent follow-up at the outpatient clinic of the bone marrow transplantation unit of the Hospital de Clínicas (Universidade Federal do Paraná) were evaluated. Patients' gender and age, time since HSCT, donor's

Financial disclosure: See Acknowledgments on page 279.

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http://dx.doi.org/10.1016/j.bbmt.2014.10.009
1083-8791/

Table 1
Demographic Data and Information Related to HSCT and Post-HSCT Periods for Patients with FA

Characteristic	Patients with Oral Manifestations of cGVHD	Patients without Oral Manifestations of cGVHD	Total
No. of patients	40 (42%)	56 (58%)	96 (100%)
Age, median (range), yr*	18 (5-32)	13 (6-42)	16 (5-42)
Gender			
Male	22 (55%)	23 (41%)	45 (47%)
Female	18 (45%)	33 (59%)	51 (53%)
Conditioning regimen			
Cyclophosphamide	20 (50%)	24 (43%)	44 (46%)
Combination chemotherapy	14 (35%)	28 (50%)	42 (44%)
Chemotherapy + total body irradiation	6 (15%)	4 (7%)	10 (10%)
Stem cell source and donor			
Related bone marrow	19 (48%)	24 (43%)	43 (45%)
Unrelated bone marrow	11 (28%)	16 (29%)	27 (28%)
Related cord blood	0 (0%)	1 (2%)	1 (1%)
Unrelated cord blood	3 (7%)	7 (12%)	10 (10%)
Unrelated peripheral blood	1 (2%)	0 (0%)	1 (1%)
Haploidentical	6 (15%)	8 (14%)	14 (15%)
Donor age, median (range), yr	19 (0-60)	13.5 (0-64)	17 (0-64)
Donor gender × patient gender			
Male × male	10 (25%)	17 (30%)	27 (28%)
Male × female	11 (28%)	12 (21%)	23 (24%)
Female × female	12 (30%)	16 (29%)	28 (29%)
Female × male	7 (17%)	11 (20%)	18 (19%)
Time after HSCT, median (range), mo	103 (3-211)	41.5 (1-261)	62.5 (1-261)
Post-HSCT period*			
Immediate (within 12 mo after HSCT)	3 (7%)	16 (29%)	19 (20%)
Intermediate (13-47 mo after HSCT)	8 (20%)	14 (25%)	22 (23%)
Late (>48 mo after HSCT)	29 (73%)	26 (46%)	55 (57%)
History of aGVHD†	10 (25%)	10 (18%)	20 (21%)
History of cGVHD*,†,‡	27 (68%)	15 (27%)	42 (44%)

aGVHD indicates acute graft-versus-host disease.
* $P < .05$.
† Data collected from medical records.
‡ cGVHD in different organs, besides the mouth.

characteristics, stem cell source, history of acute GVHD, and current medications were collected from each patient's medical records. Oral examinations were performed in the dental unit under reflective light by a dentist with experience applying the NIH scale (intrarater intraclass correlation coefficient, .969; inter-rater intraclass correlation coefficient, .934). Oral mucosa was dried with gauze and then observed for any alterations. Oral manifestations of cGVHD were scored based on diagnostics and distinctive signs according to the oral cGVHD activity assessment criteria published by the NIH [7]. The type and distribution of the lesions compatible with cGVHD were also assessed and registered in a clinical record specifically developed for this study.

Patients were excluded if they had undergone more than 1 HSCT, if the oral examination was prevented because of discomfort caused by oral cancer, or if their medical data were incomplete.

There is no standard criteria used to distinguish patients according to the time after transplantation. Based on the outpatient care standards adopted at this center and on the major complications observed after transplantation, periods in the present study were separated into 3 categories: (1) immediate post-HSCT period (up to 12 months after transplantation), the stage in which many individuals are stabilizing their immunity and blood cell count and are under immunosuppressive therapy; (2) intermediate post-HSCT period (13 to 47 months after transplantation), the stage in which most of the complications were either detected or resolved, as cGVHD often occurs in the first 3 years after the transplantation; and (3) late post-HSCT (>47 months after transplantation) period, in which patients commonly do not use any medication, and when they are usually released to their home town and came less frequently to the clinical evaluations.

Descriptive and analytic statistical analyses were performed. The chi-squared test, Fisher's exact test, and the linear trend chi-squared test were used to evaluate the association between the presence of oral manifestations of cGVHD, demographic data, and variables related to HSCT. It was considered a statistical significant association whenever $P \leq .05$. This study was approved by the ethics committee in research of the Universidade Federal do Paraná and each patient, or his/her guardian, signed an informed consent form.

RESULTS

A total of 103 individuals with FA who underwent allogeneic HSCT were evaluated. Seven patients were excluded based on the criteria described in the Materials and Methods, including 2 individuals with oral cancer. The final cohort included 96 patients (51 [53%] females and 45 [47%] males) with a median age of 16 years. Demographic data, HSCT characteristics, and GVHD data for this cohort are listed in Table 1.

Approximately 25% of the patients evaluated were receiving immunomodulatory prophylaxis or treatment for GVHD. In most cases, systemic medication was administered exclusively, and this included cyclosporine, mycophenolate mofetil, sirolimus, and prednisone alone or in combination. Five (5%) patients were applying a topical corticosteroid rinse to their oral mucosa. However, only 1 of these patients was using the topical medication exclusively.

Based on the NIH consensus criteria, 40 patients (42%) presented with oral manifestations compatible with cGVHD. Moreover, most of them presented these manifestations during the late post-HSCT period (n = 29; 73%).

According to the medical record data collected, 25% of the individuals with oral manifestations of cGVHD had previously presented with acute GVHD, and 68% had a history of cGVHD that affected several organs besides the mouth. In addition, patient age, post-HSCT period, and history of manifestations of cGVHD in other organs were found to have statistically significant associations with the presence of oral alterations compatible with cGVHD, according to the NIH consensus ($P < .001$, $P = .007$, and $P = .010$, respectively).

All patients with oral manifestations of cGVHD were classified according to the diagnostic signs exhibited, including hyperkeratotic plaques and lichenoid lesions. White plaques were observed in 95% (n = 38) of the patients with oral lesions of cGVHD. Lichenoid manifestations, atrophy, erythema, and ulcers were also identified. However, the

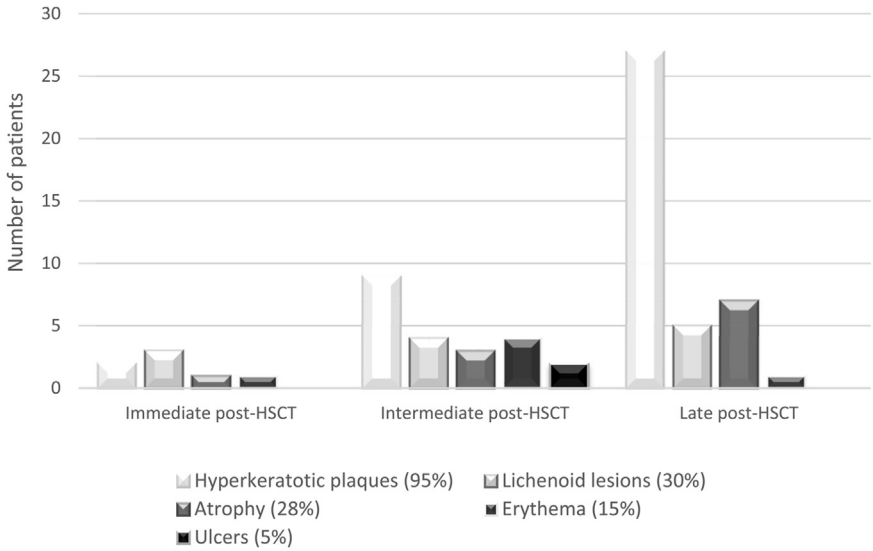

Figure 1. Prevalence and type of oral manifestations of cGVHD in patients with FA, according to time post-HSCT.

rates for these manifestations were lower. The distribution of patients with oral alterations of cGVHD according to their post-HSCT period is presented in Figure 1.

The tongue, buccal mucosa, and hard palate were the locations most involved by manifestations of cGVHD. Sites of the oral mucosa that were affected are listed in Table 2.

NIH scoring for the present cohort ranged from 0 to 10, and the average score was .82 (±1.642). When only patients with oral lesions of cGVHD were considered, the average NIH score was 1.95 (±2.074). When oral manifestations of cGVHD according to time post-HSCT period were considered, the most severe cases (indicated with a score of 10) occurred during the intermediate post-HSCT period (Figure 2).

Of the patients who presented oral manifestations compatible with cGVHD, 30 of 40 (75%) maintained persistent lesions after treatment, and 10 of 40 patients (25%) had evidence of disease activity (ie, diagnostic signs or proven distinctive signs associated with a need for treatment). The characteristics of the patients with oral manifestations of cGVHD that needed treatment are summarized in Table 3.

DISCUSSION

To our knowledge, this is the first study to evaluate oral manifestations of cGVHD in a group of patients with FA. Moreover, in contrast with other papers describing oral cGVHD, most of the individuals of this cohort were young, consistent with the observation that FA presents a low life expectancy and is commonly diagnosed during childhood.

In the present cohort, 42% of the patients developed oral manifestations compatible with cGVHD, according to the NIH consensus criteria. However, most of the individuals had favorable HSCT characteristics, such as a young age and grafted bone marrow cells obtained from a sibling, and their conditioning regimen included low doses of cyclophosphamide [11,12]. It is hypothesized that patients with FA have an increased susceptibility to cGVHD because of hypersensitivity towards substances present in the conditioning regimen. This could cause greater tissue damage and facilitate the recognition of patients' antigens by donor cells.

In a study of children who underwent HSCT, Treister et al. [13] identified a similar prevalence (36%) of oral GVHD. Fassil et al. [14] also observed oral manifestations in approximately 23% of the cGVHD patients they examined. This difference may be due to the conservative criteria utilized in the latter study, where the presence of oral lesions was only considered when the NIH scale scores were ≥3. Overall, the prevalence and incidence of alterations due to cGVHD are reported to vary from 23% to 95%, respectively [14-21].

In the present study, the distribution of oral lesions of cGVHD was found to vary widely, yet a greater involvement

Table 2
Distribution of cGVHD Lesions according to Different Sites of the Oral Mucosa

Location	Hyperkeratotic Plaques	Lichenoid Lesions	Erythema	Atrophy	Ulcers	Total
Lip	3	2	2	0	3	10
Labial mucosa	1	2	2	0	0	5
Unilateral buccal mucosa	4	0	0	0	1	5
Bilateral buccal mucosa	3	5	5	0	1	14
Unilateral retrocomissura	4	0	0	0	1	5
Bilateral retrocomissura	10	2	0	0	0	12
Tongue dorsum	14	1	1	9	0	25
Ventral tongue	0	2	1	0	1	4
Unilateral tongue border	3	3	1	1	1	9
Bilateral tongue border	1	3	0	0	0	4
Hard palate	20	0	1	0	1	22
Gingiva	6	1	0	0	0	7
Total	69	21	13	10	9	122

Mucoceles are not described in this table because none of these lesions were identified in the present cohort.

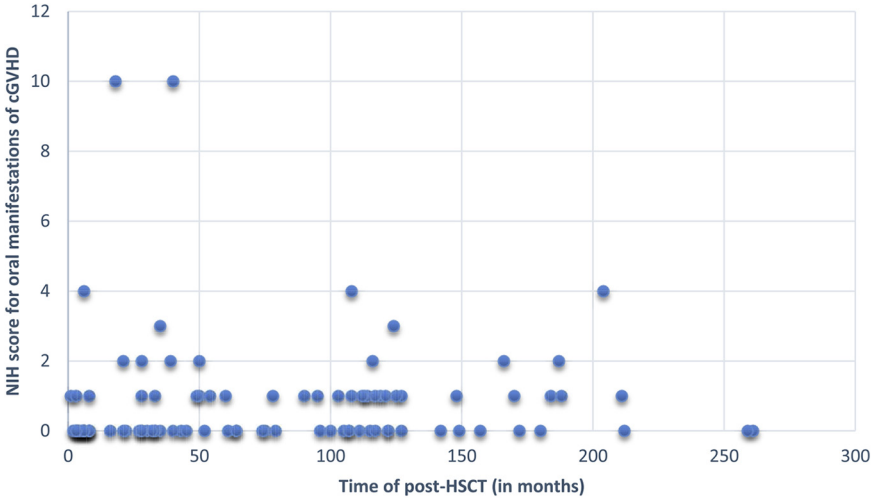

Figure 2. NIH scoring of oral manifestations of cGVHD according to the time of presentation post-HSCT.

of the buccal mucosa, tongue, and lips was observed, consistent with data reported in the literature [15,22]. However, a large number of hyperkeratotic plaques were also observed on the hard palate in this study, thereby indicating that this location should also be examined with attention during clinical examinations, particularly in patients with FA.

Lichenoid lesions were observed more frequently during the immediate post-HSCT period, ulcers were seen only during the intermediate post-HSCT stage, and the number of patients with hyperkeratotic plaques increases with time after transplantation, being observed more frequently in the late post-HSCT period (Figure 1). Although this is a cross-sectional study, the results suggest the presence of time-related changes in oral manifestations of cGVHD. Longitudinal studies are needed to evaluate the incidence and patterns of oral cGVHD over time.

Salivary glands appear to be susceptible to cGVHD because of their high expression of histocompatibility antigens and their exposure to pathogenic lymphocytes [23]. An analysis of salivary flow was not performed in this study, and none of the patients complained of xerostomia. Moreover, most of the cohort did not receive total body irradiation, which is a contributing factor to decreased salivary flow rates and symptoms of dry mouth in patients undergoing HSCT. There were also no cases of rampant caries that could be associated with the reduced saliva that was observed [24,25].

Table 3
Demographic Data and HSCT and Post-HSCT Characteristics of Patients with Oral Manifestations Compatible with cGVHD, according to Treatment

Characteristic	Patients with Oral Manifestations of cGVHD, under Treatment (active)	Patients with Oral Manifestations of cGVHD, without Treatment	Total
No. of patients	10 (25%)	30 (75%)	40 (42%)
Age, median (range), yr	14 (5-22)	19 (8-32)	18 (5-32)
Gender			
Male	4 (40%)	18 (60%)	22 (55%)
Female	6 (60%)	12 (40%)	18 (45%)
Conditioning regimen			
Cyclophosphamide	1 (10%)	19 (63%)	20 (50%)
Combination chemotherapy	5 (50%)	9 (30%)	14 (35%)
Chemotherapy + total body irradiation	4 (40%)	2 (7%)	6 (15%)
Stem cell source and donor			
Related bone marrow	1 (10%)	18 (60%)	19 (48%)
Unrelated bone marrow	5 (50%)	6 (20%)	11 (28%)
Unrelated cord blood	0 (0%)	3 (10%)	3 (7%)
Unrelated peripheral blood	1 (10%)	0 (0%)	1 (2%)
Haploidentical	3 (30%)	3 (10%)	6 (15%)
Donor age, median (range), yr	31.5 (16-37)	15.5 (0-60)	19 (0-60)
Donor gender × patient gender			
Male × male	1 (10%)	9 (30%)	10 (25%)
Male × female	5 (50%)	6 (20%)	11 (28%)
Female × female	3 (30%)	9 (30%)	12 (30%)
Female × male	1 (10%)	6 (20%)	7 (17%)
Time after HSCT, median (range), mo	24.5 (3-108)	115 (28-211)	103 (3-211)
Post-HSCT periods			
Immediate (within 12 mo after HSCT)	3 (30%)	0 (0%)	3 (7%)
Intermediate (13-47 mo after HSCT)	5 (50%)	3 (10%)	8 (20%)
Late (>48 mo after HSCT)	2 (20%)	27 (90%)	29 (73%)
History of aGVHD*	7 (70%)	3 (10%)	10 (25%)
History of cGVHD*,†	9 (90%)	18 (60%)	27 (68%)

* Data collected from medical records.
† cGVHD in different organs, besides the mouth.

Furthermore, this cohort included mostly younger patients, and they usually have less hyposalivation and a lower rate of xerostomia [13]. Mucocele was not observed in the present cohort, as well, which can be explained by the fact that they may be temporary and have often spontaneous remission.

Limited mouth opening due to sclerosis is 1 of the diagnostic signs for oral cGVHD. However, some authors suggest that restricted mouth opening is sometimes related to pain, and therefore, is not truly associated with sclerosis. Moreover, a common characteristic of patients with FA is the presence of microstomia [26], which may be another confounding factor in identifying limited mouth opening and could limit the use of the NIH scale as an index for cGVHD in patients with FA. Thus, microstomia was not evaluated in this study.

Although more than 90% of the patients in the present cohort received a low overall NIH scale score, some individuals did receive high values. In particular, the latter had ulcerated lesions, which can limit oral ingestion, compromise an individual's speaking, and negatively affect quality of life. In severe cases, systemic therapy and pain control with analgesics and anesthetic drugs may be required [7,27]. In the current study, a pain questionnaire or scale was not applied, as pain was an infrequent complaint in the clinic, which is a distinct difference from other studies [19,22,28]. Moreover, none of the patients in the current study who developed ulcers reported symptoms in their mouth or had received analgesic therapy at the time of consultation.

Many of the individuals who did not develop cGVHD treatment presented with white lesions more than 4 years after HSCT (n = 27; 90%). This observation supports the hypothesis that these lesions are not active manifestations of the disease, as cGVHD usually occurs up to the third year after HSCT [7]. It is also possible for individuals to present with conditions compatible with cGVHD after completing therapy. Therefore, we suggest that cGVHD classification should be realized not only according to temporal criteria or clinical changes, but also according to disease activity. Active oral manifestations of cGVHD are defined in the presence of diagnostic signs or certified distinctive signs of the disease with indication for therapy [14].

As expected, most of the individuals with active oral manifestations of cGVHD (in need of treatment) had undergone transplantation with features more prone to the risk of developing cGVHD, such as older and unrelated donors and more aggressive conditioning regimens, when compared with patients diagnosed with cGVHD according to the NIH consensus criteria. Moreover, although the majority of individuals (48%) diagnosed with oral cGVHD based on the NIH classification received stem cells from sibling, in the group of patients with active oral lesions, only 10% of the patients had sibling donors. Furthermore, in the active cGVHD group (10 patients under treatment) most of the individuals were in the intermediate post-HSCT period, different from those 40 patients diagnosed with cGVHD according to the NIH consensus criteria, who had undergone HSCT for 48 months or more (Tables 1 and 3).

In the present study, 75% of the patients who manifested oral changes compatible with cGVHD presented white lesions that persisted during treatment. According to the NIH consensus criteria, these oral manifestations could be considered representative of cGVHD [7], although therapeutically, they are not considered active. Currently, it is not possible to determine whether these lesions represent cGVHD manifestations versus newly isolated hyperkeratotic plaques. An oral biopsy would provide a more definitive diagnosis, although an oral cGVHD diagnosis is commonly established based on clinical manifestations. In the present cohort, all of the individuals who were diagnosed with oral manifestations of cGVHD presented sufficient clinical signs to detect cGVHD, according to the NIH consensus criteria [7]. The decision to undergo an oral biopsy was dependent on the clinical macroscopic changes. Oral erytroplakias, atrophy, or leukoplakias, which get larger and worse as time goes by, and those with a verrucous surface should be biopsied. However, stable and homogeneous hyperkeratotic plaques can be followed up. Nevertheless, evaluations should be more frequently in high-risk patients.

The NIH scale for oral manifestations of cGVHD has been validated, and despite its limitations, it is considered a tool that is easily applied. It also has a good overall reliability score, especially if the individuals performing the NIH scoring have experience with the scale and its application [29,30]. However, as a diagnostic tool, it remains to be determined whether this scale overestimates the number of patients exhibiting manifestations of cGVHD in the late post-HSCT period. Therefore, further studies should include microscopic evaluations of late lesions to determine if the lesions are manifestations of cGVHD versus hyperkeratotic changes with some degree of dysplasia and autonomous progression that are unrelated to cGVHD.

Approximately 30% of the individuals evaluated were classified as high-risk for the development of oral cancer using an algorithm that considered age, time since transplantation, and presence of oral lesions compatible with cGVHD. In particular, patients with FA who undergo HSCT and manifest cGVHD represent a high-risk group for the development of oral SCC, even at a young age and in the absence of other classical risk factors, such as smoking and alcohol consumption. For this reason, these individuals, especially those who are older and those in late post-HSCT period, should be evaluated more frequently by an oral medicine specialist as part of a screening program for oral cancer.

It is important for professionals on a transplantation team to be able to recognize the clinical characteristics of oral lesions in patients undergoing allogeneic HSCT, as this may facilitate an early diagnosis of cGVHD and the prevention of more severe stages of the disease. Furthermore, knowledge of the prevalence of these manifestations in individuals with FA is relevant to the evaluation of patients with increased risk for the development of potentially malignant disorders or malignancies in the oral cavity.

ACKNOWLEDGMENTS

The authors thank the Coordination of Improvement of Higher Education Personnel (CAPES) for support through the Graduate Program in Dentistry from the Universidade Federal do Paraná. We also thank the staff of the Bone Marrow Transplant Service from the Hospital de Clínicas (Universidade Federal do Paraná) for the opportunity to work there and study oral manifestations in patients with Fanconi anemia.

Financial disclosure: The authors have nothing to disclose..

Conflict of interest statement: There are no conflicts of interest to report.

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